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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,506	12/13/2004	Moritz Rossner	085449-0150	6374
22428 7590 01/03/2008 FOLEY AND LARDNER LLP SUITE 500 3000 K STREET NW WASHINGTON, DC 20007			EXAMINER SWOPE, SHERIDAN	
			ART UNIT 1652	PAPER NUMBER
			MAIL DATE 01/03/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/507,506	Applicant(s) ROSSNER ET AL.	
	Examiner Sheridan L. Swope	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 61-127 is/are pending in the application.
- 4a) Of the above claim(s) 61-85 and 89-122 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 86-88 and 123-127 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' response on September 20, 2007, to the First Action on the Merits of this case mailed April 20, 2007, is acknowledged. It is acknowledged that applicants have amended Claims 86-88 and added Claims 123-127. Claims 61-127 are pending. Claims 123-127 are encompassed by the elected invention. Claims 61-85 and 89-122 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 86-88 and 123-127 are hereby considered.

Drawings-Objections

Objection to Figures 24 and 25 for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO:), as explained in the prior action, is maintained. As explained in the prior action, the sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Applicant is required to check the disclosure completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

Abstract- Objections

The abstract is objected to for being a single, run-on sentence.

Specification-Objections

The specification is objected to for having two sets of figure legends.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claims

It is noted that in Applicants' remarks, they have inserted the phrase "We claim", as the first line of the claim set (pg 25).

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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Claims 123 and 125-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claims 123 and 125-127, reference to specific amino acid residues, without reference to a specific sequence by SEQ ID NO, renders the claim indefinite. The skilled artisan would not know the metes and bounds of the recited invention.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 86-88 and 123-127 are rejected under 35 U.S.C. 112, first paragraph. The specification in combination with the prior art is enabling for a method of detecting protein/protein interaction using fusion proteins that, upon binding, reconstitute the activity of the TEV protease of Bazan et al, 1988 and, thus, activate a reporter construct comprising a specific cleavage motif (see rejection under 103(a)). However, the specification does not reasonably provide enablement for a method of detecting protein/protein interaction using fusion proteins comprising fragments of any TEV protein to activate any reporter construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400

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(Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 86-88 are so broad as to encompass a method for detecting protein/protein interaction using fusion proteins comprising any fragments of any TEV protease, wherein any reporter construct is activated by TEV protease cleavage. Claims 123-127 are so broad as to encompass a method for detecting protein/protein interaction using fusion proteins comprising specific fragments of any TEV protease, wherein a reporter construct is activated by TEV protease cleavage. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods using a large number of possible fragments of any TEV protease having any structure as well as a large number of reporter constructs comprising motifs cleavable by any said TEV proteases, as broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired TEV protease activity, reconstitution of activity upon binding, and reporter constructs cleavable by said any TEV protease requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any,

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are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function.

However, in this case the prior art is enabling for using the TEV protease of Bazan et al in the method described under 103(a) below.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 86-88, which encompasses a method for detecting protein/protein interaction using fusion proteins comprising any fragments of any TEV protease and any reporter construct cleavable by any said TEV protease. The specification does not support the broad scope of Claims 123-127, which encompasses a method for detecting protein/protein interaction using fusion proteins comprising specific fragments of any TEV protease and any reporter construct cleavage by any said TEV protease. The specification does not support the broad scope of Claims 86-88 and 123-127 because the specification does not establish: (A) the structure/sequence of any protein having TEV protease activity that can be use in the recited method; (B) regions of the protein structure which may be modified without affecting the TEV protease activity or the ability to be reconstituted upon

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fusion protein association; (C) the general tolerance of the TEV protease activity and the ability to be reconstituted upon fusion protein association to modification and extent of such tolerance; (D) regions of any reporter construct which may be modified without affecting ability to be cleaved and activated by any TEV protease; (E) the general tolerance of ability to be cleaved and activated by any TEV protease to modification and extent of such tolerance; (F) a rational and predictable scheme for modifying any residues in either the TEV protease, the fusion proteins, or the reporter construct with an expectation of obtaining the desired biological functions; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods using any protein having TEV protease activity, wherein the activity can be reconstituted upon fusion protein association and, thus activate any reporter construct by TEV cleavage. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 86-88 and 123-127 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of methods for detecting protein interaction in a cell using a first and second fusion protein comprising domains of any TEV protease and any reporter that can be cleaved and activated by any said TEV protease. The specification teaches only a single representative species of such methods; however, the specification fails to teach the structure/sequence of the TEV protease used. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of methods for detecting protein interaction in a cell using a first and second fusion protein comprising domains of any TEV protease and any reporter. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claims 86-88 under 35 U.S.C. 103(a) as being unpatentable over Michnick et al, 2000 in view of Bazan et al, 1988 and further in view of Carmel et al, 1973 as evidenced by Stevens, 2000 and Sawyer et al, 1978, for the reasons explained in the prior action, is maintained.

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In support of their request that said rejection be withdrawn, Applicants provide the following arguments. Reference to Bazan for the alleged teaching that “like elastase, the structure of TEV protease has twin β -barrel trypsin-like folds” is not sound. More importantly, the skilled artisan would not be motivated to use TEV protease in the claimed method merely based on a structural similarity with elastase. The Examiner is merely using hind-sight reasoning.

These arguments are not found to be persuasive for the following reasons. Bazan et al teach a group of cysteine-active-center enzymes that are homologous to trypsin-like serine proteases; comprising twin β -barrel trypsin-like folds (Abstract). Bazan et al further teach that both TEV protease and elastase comprise said twin β -barrel trypsin-like folds (Fig 2 & 3). For TEV protease, the twin β -barrel structure separates the conserved catalytic histidine and aspartic acid residues from the conserved catalytic cysteine residue by a hinge regions (Fig 2). Such a structure provides motivation to make and use two fusion proteins, each comprising a single β -barrel structure, for assaying protein/protein interaction. For these reasons and those presented in the prior action, rejection of Claims 86-88 under 35 U.S.C. 103(a) as being unpatentable over Michnick et al, 2000 in view of Bazan et al, 1988 and further in view of Carmel et al, 1973 as evidenced by Stevens, 2000 and Sawyer et al, 1978, is maintained.

Allowable Subject Matter

No claims are allowable

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to reject amended claims or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37

CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943.


The examiner can normally be reached on M-F; 9:30-7 EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1652



SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER